Amendments to the Claims:

1. (Currently Amended) A method of screening for an agent ~~to determine its usefulness~~ having efficacy in treating a condition characterised by pancreatic islet or β-cell dysfunction, the method comprising:

~~(a) identifying proteins which are differentially expressed in biological samples obtained from subjects having reduced or increased pancreatic islet or β-cell function and normal subjects, said samples being obtained before and after treatment of said subjects with a compound which alleviates or improves pancreatic islet or β-cell dysfunction;~~

~~(b) providing a biological sample of tissue or cells which undergo a biological change in response to the action of insulin;~~

~~(c) contacting the sample of step b) with said agent and identifying proteins which are differentially expressed in response to said agent; and,~~

~~(d) comparing the results of a) and c) thereby identifying those agents which alter the expression levels of said proteins towards that of a subject having substantially normal pancreatic islet or β cell function.~~

(a) providing

(i) a first biological sample obtained from a subject having pancreatic islet or β-cell dysfunction,

(ii) a second biological sample obtained from a normal subject,

(iii) a third biological sample from a subject having pancreatic islet or β-cell dysfunction who has been treated with a known treatment or compound which alleviates or improves pancreatic islet or β-cell dysfunction, and

(iv) a fourth biological sample obtained from a normal subject who has been treated with said known treatment or compound;

(b) identifying at least one differentially expressed

protein which is:

(i) differentially expressed in said first and second biological samples;

(ii) differentially expressed in said first and third biological samples; and

(iii) not differentially expressed in said second and fourth biological samples or differentially expressed in said second and fourth biological samples to a lesser degree than in said first and third biological samples;

(c) providing a fifth biological sample which undergoes a biological change in response to insulin action obtained from a subject having pancreatic islet or β-cell dysfunction, wherein said fifth biological sample has been treated with said agent or said subject having pancreatic islet or β-cell dysfunction has been treated with said agent; and

(d) determining the level of expression of said at least one differentially expressed protein in said fifth biological sample to identify an agent which alters the expression level towards that observed in said second or third biological sample, thereby identifying an agent having efficacy in treating pancreatic islet or β-cell dysfunction.

2. (Cancelled)

3. (Cancelled)

4. (Previously Presented) The method of claim 1, wherein the pancreatic islet or β-cell dysfunction is a result of a disorder which causes a reduction in pancreatic islet or β-cell mass and/or a reduction in a pancreatic islet or β-cell biological activity.

5. (Currently amended) The method of claim 1, wherein said subjects having ~~reduced or increased~~ pancreatic islet or β-cell dysfunction are non-insulin dependent diabetic subjects.

6. (Currently Amended) The method of claim 1, wherein ~~the~~ said samples comprise ~~comprises~~ pancreatic islets.

Claims 7-11 (Cancelled)

12. (Currently Amended) The method of claim 1, wherein the subjects having ~~reduced or increased~~ pancreatic islet or β-cell dysfunction are animals which have non-insulin dependent diabetes as a result of a genetic mutation, said animals being selected from the group consisting of ob/ob, db/db, agouti, fat, and fa/fa mice ~~lean~~.

13. (Currently amended) The method of claim 1, wherein said ~~reduced or increased~~ pancreatic islet or β-cell dysfunction is exacerbated by dietary treatment.

14. (Currently amended) The method of claim 1, wherein said subjects having ~~reduced or increased~~ pancreatic islet or β-cell dysfunction are the offspring of pregnant animals fed on a reduced protein diet.

15. (Original) The method of claim 14, wherein the diet fed to the offspring post weaning is additionally a high fat diet.

16. (Currently amended) The method of claim 1, wherein said subjects having ~~reduced or increased~~ pancreatic islet or β-cell dysfunction are desert rodents selected from the group consisting of spiny mice and sand rats which develop diabetes on normal laboratory diets but remain normoglycaemic on their natural diet.

17. (Currently amended) The method of claim 1, wherein said subjects having ~~reduced or increased~~ pancreatic islet or β-cell dysfunction are animals which have gender selective

differences in pancreatic islet or β-cell mass.

18. (Currently Amended) The method of claim 1, wherein said subjects are selected from the group consisting of ~~the differential protein expression is compared in closely related animals, such as~~ C57BI/6 and C57BI/Ks mice ~~which show differences in pancreatic islet or β-cell mass in response to said treatment~~.

19. (Previously Presented) The method of claim 4, wherein differential levels of islet cell or β-cell mass or function are induced by modifying the diet of pregnant animals or by comparing pregnant and non-pregnant animals.

20. (Currently Amended) The method of claim 1, wherein the subjects having pancreatic islet or β-cell dysfunction have reduced levels of pancreatic islet or β-cell function.

21. (Previously Presented) The method of claim 20, wherein said reduced pancreatic islet or β-cell function is the result of non-insulin dependent diabetes (type 2 diabetes), syndrome X (insulin resistance syndrome) or gestational diabetes.

22. (Currently Amended) The method of claim 1, wherein the subjects having pancreatic islet or β-cell dysfunction have a higher than normal level of pancreatic islet or β-cell function.

23. (Original) The method of claim 22, wherein the higher levels of pancreatic islet or β-cell function in the subjects are obtained by treatment with an insulin sensitiser drug, dietary restriction or exercise.

24. (Currently Amended) The method of claim 23, wherein the insulin sensitising drug is a thiazolidinedione insulin

sensitiser.

25. (Original) The method of claim 24, wherein the thiazolidinedione insulin sensitiser is rosiglitazone (BRL 49653).

26. (Original) The method of claim 23, wherein the insulin sensitiser drug is a non-thiazolidinedione acting as an agonist or partial agonist of the PPAR gamma nuclear receptor.

27. (Original) The method of claim 23, wherein the insulin sensitiser drug is a β-3-adrenoceptor agonist or leptin.

28. (Original) The method of claim 22, wherein the subjects having a higher than normal level of pancreatic islet or β-cell function are pregnant animals.

29. (Original) The method of claim 22, wherein the higher level of pancreatic islet or β-cell function in the subjects are obtained by administration of an insulin secretagogue peptide or drug.

30. (Original) The method of claim 29, wherein the insulin secretagogue is GLP-1 or a stable GLP-1 analogue or exendin 4.

31. (Currently Amended) The method of claim 23, wherein the insulin ~~secretagogue~~ sensitizer drug further stimulates insulin production and/or the genesis of islet cells.

32. (Previously Presented) The method of claim 1, said differential expression is established using two-dimensional gel electrophoresis carried out on said biological samples.

33. (Currently Amended) The method of claim 1, further comprising the step of isolating [[a]] said at least one

differentially expressed protein identified in the method.

34. (Currently Amended) The method of claim 33, further comprising the step of characterising the at least one isolated protein.

35. (Currently Amended) The method of claim 1, wherein the at least one differentially expressed protein ~~or proteins~~ comprise at least one selected from the group consisting of POM6, POM7 POM8, POM9, POM10, POMT1, POMT2, POMT3, POMT4, POMT5, POMT11, POMT12, POMT13, PSEM14 AND PSEM15.

36-38. (Cancelled)

39. (Previously Presented) A method of making a pharmaceutical composition which comprises having identified an agent using the method of claim 1, the further step of manufacturing the agent and formulating it with an acceptable carrier to provide the pharmaceutical composition.

40-43. (Cancelled)

44. (Withdrawn) A method of treating a condition characterised by islet or β-cell dysfunction in a patient, the method comprising administering to the patient a therapeutically or prophylactically effective amount of an agent identified by a method of claim 1.

45. (Withdrawn) The method of claim 44, wherein the pancreatic islet or P-cell dysfunction is a result of non-insulin dependent diabetes or type 2 diabetes, syndrome X or insulin resistance syndrome or gestational diabetes.

46. (Cancelled)

47. (Currently Amended) The method of claim 1, wherein ~~the~~ said samples ~~is~~ are selected from the group consisting of a tissue sample, cells, ~~or~~ body fluid, and ~~sample or~~ urine.

48. (Currently amended) The method of claim 1 wherein at least four proteins are identified as differentially expressed in said subjects having ~~reduced or increased~~ pancreatic islet or β cell dysfunction thereby providing a multi-protein fingerprint of the pancreatic islet or β-cell dysfunction.

49. (Cancelled)

50. (Withdrawn) A method of treatment by the use of an agent that will restore the expression of one or more differentially expressed proteins in the pancreatic islet or β-cell dysfunction state to that found in the normal state in order to prevent the development of non-insulin dependent diabetes in a pre-diabetic subject.

51. (Withdrawn) A method whereby the pattern of differentially expressed proteins in a tissue sample or body fluid sample or urine of an individual with pancreatic islet or β-cell dysfunction is used to predict the most appropriate and effective therapy to alleviate the pancreatic islet or β-cell dysfunction state and to monitor the success of that treatment.

52. (Withdrawn) The method of claim 51 whereby the pancreatic islet or β-cell dysfunction state is non-insulin dependent diabetes or type 2 diabetes.

53. (Withdrawn) A protein which is differentially expressed in relevant tissue from, or representative of subjects having differential levels of pancreatic islet or β-cell dysfunction and which is as obtainable by the method of two-dimensional

gel electrophoresis carried out on said tissue or a protein-containing extract thereof, the method comprising:

(a) providing non-linear immobilized pH gradient (IPG) strips of acrylamide polymer 3 mm x 180 mm;

(b) rehydrating the IPG strips in a cassette containing 25 ml. of an aqueous solution of urea (8M), 3-[(cholamidopropyl) dimethylammonio]-1-propanesulphonate (CHAPS, 2% w/v), dithioerythritol (DTE, 1OmM), mixture of acids and bases of pH 3.5 to 10 (2% w/v) and a trace of Bromophenol Blue ;

(c) emptying the cassette of liquid, transferring the strips to an electrophoretic tray fitted with humid electrode wicks, electrodes and sample cups, covering the strips and cups with low viscosity paraffin oil;

(d) applying 200 micrograms of an aqueous solution of dried, powdered material of the relevant body tissue in urea (8M), CHAPS (4% w/v), Tris (40 mM), DTE (65 mM), SDS (0.05% w/v) and a trace of Bromophenol Blue to the sample cups, at the cathodic end of the IPG strips;

(e) carrying out isoelectric focusing on the gel at a voltage which increases linearly from 300 to 3500 V during 3 hours, followed by another 3 hours at 3500 V, and thereafter at 5000V for a time effective to enable the proteins to migrate in the strips to their pI- dependent final positions;

(f) equilibrating the strips within the tray with 100 ml of an aqueous solution containing Tris-HCl (50 mM) pH 6.8, urea (6M), glycerol (30% v/v), SDS (2% w/v) and DTE (2% w/v) for 12 minutes;

(g) replacing this solution by 100 ml. of an aqueous solution containing Tris-HCl (50 mM) pH 6.8, urea (6M), glycerol (30% v/v), SDS (2% w/v), iodoacetamide (2.5% w/v) and a trace of Bromophenol Blue for 5 minutes;

(h) providing a vertical gradient slab gel 160 x 200 x 1.5 mm of acrylamide/piperazine-diacrylyl cross- linker (9-16% T/2. 6% C), polymerised in the presence of TEMED (0.5% w/v),

ammonium persulphate (0.1% w/v) and sodium thiosulphate (5 mM), in Tris-HCl (0.375M) pH 8.8 as leading buffer;

(i) over-layering the gel with sec-butanol for about 2 hours, removing the overlay and replacing it with water ;

(j) cutting the IPG gel strips to a size suitable for the second dimensional electrophoresis, removing 6 mm from the anode end and 14 mm from the cathode end;

(k) over-layering the slab gel with an aqueous solution of agarose (0.5% w/v) and Tris-glycine-SDS (25 mM-198 mM- 0.1% w/v) as leading buffer, heated to 70°C and loading the IPG gel strips onto the slab gel through this over- layered solution;

(l) running the second dimensional electrophoresis at a constant current of 40 mA at 8-12°C for 5 hours; and

(m) washing the gel.

54. (Withdrawn) The protein of claim 53, wherein the protein is selected from POM6, POM7, POM8, POM9, POM10, POMT1, POMT2, POMT3, POMT4, POMT5, POMT11, POMT12, POMT13, PSEM14 AND PSEM15.

55. (Withdrawn) A differentially expressed protein having one or more of the identifying characteristics as set out in Table 2.

56. (Withdrawn) The protein of claim 55, wherein the identifying characteristics are pI and Mw.

57. (Withdrawn) The method of claim 44, wherein said agent is a protein selected from POM6, POM7, POM8, POM9, POM10, POMT1, POMT2, POMT3, POMT4, POMT5, POMT11, POMT12, POMT13, PSEM14 and PSEM15.